COPY

REMARKS

Claims 1-8, 14-18, and 26-35, are pending in the present application. Support for antibodies can be found throughout the specification as filed, such as in Example 9. Support for the recitation of "healthy or asymptomatic donor" can be found throughout the specification as filed. The specification is directed to using binding agents in a blood bank setting and donors in this field must be healthy or asymptomatic to in order to be able to donate blood. Thus, it is an art-recognized term meaning that the subject is either healthy, or has a low level of bacterial contamination which does not cause symptoms (i.e., asymptomatic). We provide herewith a declaration by one of skill in this art, Dr. Harvey Klein, a leader in the field of transfusion medicine stating that the term "donor" is a standard, art-recognized term. Applicants submit that no new matter has been added by this amendment. Applicants reserve the right to pursue any canceled subject matter in future applications.

Applicants thank Examiners Hines and Elliot for the telephonic interview of November 21, 2003, during which the claims, and the cited art were discussed. Applicants further thank Examiners Hines and Elliot for the interview of September 9, 2003, during which certain proposed claim amendments and a draft declaration comparing Applicants antibodies with commercially available antibodies were discussed. Issues raised in the Office Action are addressed below in the order they were raised by the Examiner.

1. Applicants note that the amendment filed August 13, 2003, has been entered. Claims 1-8, 14-15, 23 and 25-35 are pending.

2. Applicants note with appreciation the withdrawal of the rejections of record under 35 U.S.C. §103.

3. Claims 1-8, 14-18, 23 and 25-35 are rejected under 35 USC §112, first paragraph, as allegedly failing to "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims." [Office Action at page 3]. In particular, the Examiner alleges that "[t]he specification only teaches pan-generic monoclonal antibodies that specifically binds to the gram-positive bacterial antigen lipoteichoic acid clone 96-100 and/or a pan-generic monoclonal antibody that

PAGE 8/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

specifically binds to the gram negative bacterial antigen Lipid A clone 26-5." [Office Action at page 4, lines 3-6].

Preliminarily, it appears that the Examiner means that the specification is enabling only for a monoclonal antibody clone 96-110 (IgG1) that binds the gram positive bacterial antigen lipoteichoic acid and a monoclonal antibody clone 26-5 (IgG2b) that binds to a gram negative bacterial agent, Lipid A. See Example 9. Applicants respectfully traverse this rejection for the reasons set forth below:

First, the application discloses how to make and/or screen for antibodies that are capable of pan-generic cross-reactivity to diverse bacterial species and are capable of detecting clinically relevant amounts of bacterial contaminants in blood or blood products. Example 9, provides examples of specific binding agents having the desired characteristics. In addition, the specification describes how to make antibody derivatives using standard art-recognized techniques at page 24, line 16-26 and page 25-26. Furthermore, the application teaches methods for selecting and optimizing antibodies that may be used in the claimed assays.

It is Applicant' position that in this case, the key to obtaining the antibodies as claimed lies in the screening and selection process as set forth throughout the specification as filed. *See*, for example, lines 16-26 of page 24; and lines 6-15 of page 25; and lines 3-22 of page 26. Once the skilled artisan has the benefit of the teachings of the instant application and realizes that antibodies having pan-generic cross-reactivity and sensitivity are useful in screening for clinically relevant amounts of bacterial contaminants, it would be a matter of routine experimentation to screen for other antibodies having similar properties.

Secondly, subsequent to filing the application, Applicants have both made and screened for additional antibodies using the experimental methods described in the specification that meet the desired properties. *See* the accompanying Declaration under 37 C.F.R. § 1.132 by Dr. Jeff Hall. Applicants have provided objective data demonstrating that the Verax antibodies[1] identified using the screening process as described in the application are pan-generic and capable of detecting clinically relevant amounts of bacteria.

PAGE 9/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

Thirdly, as early as 1986, the Court of Appeals Federal Circuit has held that obtaining monoclonal antibodies by the hybridoma process taught by Milstein and Kohler as well as screening methods to identify antibodies possessing certain desired characteristics, including affinity, was well known in the art and did not constitute an undue experimentation for a person skilled in the art of antibodies. *See, Hybritech Inc., v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (CAFC 1986).

Finally, solely in an effort to expedite prosecution, Applicants have cancelled claims 23 and 25 and amended the remaining claims to recite the term "antibodies" instead of binding agents. Applicants reserve the right to pursue the cancelled subject matter in a future continuation or divisional applications.

In sum, methods for making and/or screening for antibodies having desired properties does not rise to the level of undue experimentation and reconsideration and withdrawal of this rejection is respectfully requested.

4. Claims 1, 3-6, 14, and 16 and 23-24 are rejected under 35 USC §103(a) as allegedly being unpatentable over McLaughlin (of record), Erich et al. (*J. Immunol.* 143(12): 4053-4060 (1989)), Tadler *et al.* (of record), and Fisher et al. (WO 98/57994). In particular, the Examiner states that "it would have been prima facie obvious to modify the analyte detection immunoassay that incorporates a set of binding agents as taught by McLaughlin and Tadler et al., since McLaughlin and Tadler et al., teach antibodies which specifically bind to gram-negative or gram-positive bacteria in order to determine their presence and/or absence wherein the assay is modified to include the pan-generic monoclonal antibodies as taught by Erich et al., and Fischer et al." [Office Action at page 10]. Applicants respectfully traverse this rejection. Applicants will show that the combination of references fails to: (A) provide motivation or reasonable expectation of success; and fails to (B) provide the claimed invention.

[1] Verax antibodies include antibodies that are disclosed in Example 9 and antibodies that

PAGE 10/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

Lack of Motivation & Reasonable Expectation of Success

In making the combination, the Examiner admits that McLaughlin fails to teach a pan-generic monoclonal antibody that specifically binds to the gram-negative bacterial antigen Lipid A clone 26-5[2] but argues since Erich et al. disclose a monoclonal antibody that shows extensive cross-reactivity with heat killed as well as live gram negative bacteria the skilled artisan would be motivated to modify the assay to include the antibody as taught by Erich et al. [Office Action at page 7]. Similarly, the Examiner admits that Tadler et al. fails to teach the use of a monoclonal antibody 96-110[3] but argues since Fischer et al. disclose a monoclonal antibody designated as 96-110 that exhibited strong IgG reactions the skilled artisan would be motivated to modify the assay to include the antibody as taught by Fischer et al. [Office Action at page 8-9]. Applicants respectfully submit that this rejection is legally insufficient in that:

(a) there is no suggestion or motivation in the cited art to modify the claimed assay to use either the McLaughlin or the Tadler antibodies to begin with;

(b) there is no suggestion or motivation in the cited art to modify an assay to substitute the McLaughlin antibodies with the Erich antibodies or to substitute the Tadler antibodies with the Fischer antibodies as suggested by the Examiner; and

(c) there is no reasonable expectation leading one to believe that such a combination would result in an effective test for detecting less than 1 x 10^6 CFU per mL of bacterial contaminants.

~~Applicants have previously addressed the deficiencies presented by the McLaughlin and~~ Tadler et al. antibodies in our responses dated October 8, 2002 and April 11, 2003 and in our draft Declaration presented during the Interview dated September 9, 2003. We incorporate herein the arguments presented against these references in our previous responses. In addition,

---

were generated and/or screened for using the methods taught in the specification.

[2] Presumably, the Examiner means a monoclonal antibody (clone 26-5) that specifically binds to the gram-negative bacterial antigens.

[3] Presumably, the Examiner means a monoclonal antibody (clone 96-110) that specifically binds to the gram-positive bacterial antigens.

PAGE 11/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

we submit an executed Declaration which compares the Verax antibodies with commercially available antibodies that are marketed as being pan-generic in nature. Furthermore, we respectfully submit that the Examiner has admitted on record that the Tadler et al. antibodies and the McLaughlin antibodies are not pan-generic in nature and has withdrawn rejections based on these references. Therefore, preliminarily, we see no reason why the skilled artisan would modify the claimed assay to use the Tadler et al. and McLaughlin antibodies to begin with.

Assuming arguendo, the skilled artisan were to use the antibodies disclosed by Tadler et al. and McLaughlin in the claimed assay, we believe that there is no suggestion or motivation in the cited art to modify the assay as suggested by the Examiner. McLaughlin teaches an antibody that is capable of detecting Salmonella, Neisseria, and Chlamydia.[4] As stated above, the Examiner agrees that this antibody is not pan-generic in nature. The Examiner then substitutes the Erich antibodies for the McLaughlin antibodies. However, a close review of Erich et al shows that the Erich et al. antibodies at best react with two (live) bacterial genera: Escherichia and Salmonella. See Table VI. In addition, these antibodies react with the LPS of three heat-killed bacterial genera: Escherichia, Shigella and Salmonella. In effect, the Examiner substitutes an antibody that is cross-reactive with three bacterial genera with another antibody that is also cross-reactive with three *albeit* different bacterial genera. It is Applicant's position that the skilled artisan would not be motivated to make the substitution suggested by the Examiner because Erich et al. fails to provide any reasons for the skilled artisan to do so.

Similarly, the Examiner admits that Tadler et al fails to disclose a pan-generic antibody. In fact, the Tadler et al. antibody shows binding and detection of four (4) bacterial genera: the *Streptococcus* species, *Staphylococcus* species, Enterococcal species, and Clostridium species, but does not indicate the level of detection. See Table 1. However, Tadler et al. only show

[4] The Examiner contends that McLaughlin teaches the "immunological detection of an entire class of microorganism." Office Action at page 6. We note that this characterization is erroneous. Because McLaughlin actually states that based on the discovery of antibodies that bind to three species "*it is now possible to* perform a single test for a large number of LPS producing organisms merely by reacting said antibody with a clinical reaction" (see column 5, lines 29-34). [emphasis added]. Applicants assert that although McLaughlin states that it would be possible to perform a single test, McLaughlin *did not* actually perform the tests. The courts have held that "obvious to try" is not the standard for an obviousness rejection. *In re O'Farrell*, 853, F.2d 894, 903, 7 USPQ 2d 1673, 1681 (Fed. Cir. 1988).

PAGE 12/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

detection of *S. mutans* and *S. epidermidis* at clinically relevant levels of 1 x 10^6 colony forming units (CFU) per milliliter (mL). See Figure 2. In total, Tadler et al. show detection of two bacterial genera at clinically relevant amounts as required by the claims. The Examiner then substitutes the Tadler et al. antibody with the Fisher et al. antibody to make up for the deficiencies of the Tadler antibodies. However, a review of the Fisher et al. reference shows that Fischer et al disclose binding to ***only*** one bacterial genus: the Staphylococcus genus. The Fisher reference discloses that the antibody is capable of treating infections of seven (7) species of Staphylococcus, *S. epidermidis*, *S. hemolyticus*, *S. mutans*, *S. hominus*, *S. aureus*, *S. faecalis*, and *S. pyogenes* (see the Figures). In effect, the Examiner substitutes an antibody that is cross-reactive with least two bacterial species at clinically relevant amounts with another antibody that taught to be cross-reactive with just one bacterial genus. It is Applicant's position that based solely on the teachings of the Fischer reference a skilled artisan would not be motivated to make the substitution suggested by the Examiner because Fischer et al. fails to provide any reasons to do so.

Applicants respectfully submit that Courts have cautioned against the use of the patentees disclosure as a blueprint to reconstruct the invention from the prior art. See *Interconnect Planning Corp. v. Feil, 227 USPQ 543 (Fed. Cir. 1985).* Applicants specification teaches the unappreciated properties of the Fischer antibody. See Example 9. These properties were further highlighted during the Interview dated September 9, 2003. However, there is no teaching, disclosure, or suggestion of these properties in the Fischer reference. Accordingly, the teachings of the Fischer reference, the *only* teachings that may be legally relied upon, fails to provide any motivation for the combination suggested by the Examiner. The following Table provides a comparison between the properties of the Fischer antibody taught in the Fischer reference and the properties as taught by the instant application:

Gram positive bacterial species recognized by the Fisher antibody as taught by the Fischer reference	Gram positive bacterial species recognized by the Fisher antibody as taught by the instant application
Staphylococcus spp.	*Staphylococcus spp.* *Streptococcus pyogenes* *Group B Streptococcus*

PAGE 13/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

	Group G Streptococcus *Enterococcus faecalis* *Corynebacterium minutissimum* *Clostridium perfringens* *Bacillus spp.*

As can be seen from the Table, there is no objective evidence or suggestion in the Fisher publication that the antibodies would be reactive outside of Staphylococcus, nor is there any teaching that the antibody would be effective in a blood bank setting for detection of clinically relevant amounts of bacteria. Any pan-generic activity of the Fisher antibody was completely unappreciated in the PCT publication. Moreover, it is well settled law that "a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination." *Smithkline Diagnostics v. Helena Laboratories Corp.*, 859 F.2d 878, 886-87, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988). In other words, in deciding that a novel combination/method would have been obvious, there must be supporting teaching in the prior art. The Federal Circuit has often stated that "[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

Failure to provide the Claimed Invention

It is Applicant's position that the proposed combination of references fails to teach or suggest all the limitations of the claims. See In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q 494, 496 (C.C.P.A. 1970). The claims as currently amended require three key elements: (1) screening of donor blood, blood products, and tissue, (2) pan-generic activity of the antibodies, and (3) detection of clinically relevant amounts of bacteria.

A person skilled in the art of blood banking would recognize that there is a distinct difference in diagnostic assays to identify specific bacteria and screening blood or blood products from healthy and/or asymptomatic donors for bacteria where it is not known *apriori* whether the donated blood sample: is or is not contaminated; and if contaminated what the bacterial contaminants might be.

PAGE 14/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

Each reference cited by the Examiner, McLaughlin, Erich, Tadler, and Fisher, teach either the identification of specific bacteria, or administration of an antibody in a therapeutic setting to kill a specific bacteria. There are no teachings or suggestions in any of the references that the antibodies could be used in the manner as currently claimed (wherein the antibodies are truly pan-generic). None of the references teach or suggest even trying to test blood, blood product, or tissue taken from healthy or asymptomatic donors as is required by the claims.

It is well known in the Blood Banking industry that only healthy and asymptomatic persons are allowed to donate blood. Prior to donating, each individual must undergo a thorough screening process that includes temperature, iron levels in the blood, and questions about lifestyle habits and travel outside the United States to countries known to have populations infected with various diseases. If the donor fails any of these requirements, the individual is turned away from the donation center to prevent contamination of the recipients. Often, donors are asymptomatic for infection and donate blood, which is then stored for use. Most contaminants arise from the collection process (e.g., skin introduced into the collection as a result of needle puncture, environmental factors, hair follicles, etc.). Occasionally, subclinical levels of bacteria at the time of donation can expand to levels such that they would cause infection when often transferred to a recipient. The instant claims are directed to method for testing the blood obtained from such healthy or asymptomatic donors for bacterial contamination.

Preamble in Method Claims must be given Patentable Weight

The Examiner argues that that the preamble of the instant claims has not been given patentable weight. Applicants respectfully disagree. The courts have held that in the case of method claims, the preamble is given patentable weight when it breathes life and meaning into the claims. In *Griffin v. Bertina*, 62 USPQ2d 1431 (CAFC 2002), the preamble was directed to a method of diagnosing wherein the diagnosis is again stated in the body of the claim, thus diagnosis was considered to be the essence of the invention and gives "life and meaning" to the manipulative steps. See *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). The instant claims parallel *Griffin v. Bertina* in that the preamble recites a method of screening donor blood, blood products, and tissue for clinically relevant amounts of bacteria, the method

PAGE 15/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

steps are directed specifically to carrying out the screening, and when found to be free of clinically relevant amounts of bacteria, the claim body recites that the donor blood, blood products, and tissue is useful for transfer to a recipient. Thus, Applicants assert that the preamble of the currently amended claims gives life and meaning to the manipulative steps and should be properly accorded patentable weight.

Secondary Considerations

(a) Unexpectedly superior results

Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Jeff Hall that compares the antibodies that were either taught in Example 9 or that were subsequently made in accordance with the teachings of the specification with commercially available antibodies that are being marketed as being pan-generic in nature. The Declaration shows the superior cross-reactivity to diverse bacterial species and sensitivity of the disclosed antibodies.

(b) Skepticism in the art

As discussed in our previous responses, those of skill in this art were skeptical about the effectiveness of immunoassay-based tests because of the lack of common bacterial antigens across the diverse bacterial species. To this end, we highlight excerpts from Stephen Wagner, (*Int. J. Med. Microbiol. Virol. Parasitol. Infect. Dis.* 283(3): 253-257) article that states:

> [N]o practical test is available for bacteria detection in donor blood. Development of a bacterial test will be a formidable task, and will not likely parallel the antibody-based ~~tests frequently used for detection of viral infections (see page 253).~~ None of the methods for detecting bacterial contamination are feasible for immediate implementation (see page 255). Detection of bacterial antigens represent an interesting potential method. One difficulty of developing immunological-based tests is that there are likely to be no common antigens on the surface of the diverse species that have been implicated in transfusion-associated sepsis. No practical methods are available for detecting bacteria which can routinely implemented. One of the problems in reducing transfusion-associated bacterial sepsis is that a broad range of species with vastly different surface properties may be present (page 256).

(c) Long-felt need and failure of others

PAGE 16/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

In previous replies, Applicants have clearly set forth the failure in the field of blood banking throughout the 1990s to generate an effective test as required by blood banks. Thus, there remains a long-felt need for a rapid and effective test to test for clinically relevant levels of bacteria immediately prior to transfer to a recipient. Applicants provide herewith a Declaration by Dr. Harvey Klein, Chief of the Department of Transfusion Medicine at the Warren C. Magnuson Clinical Center, National Institutes of Health who has been working in the field of transfusion medicine for over twenty (20) years setting forth the long-felt need in the industry together with the failure of others. Applicants respectfully submit that "the failure of others to satisfy a long-felt need or develop a commercially successful product is evidence of non-obviousness. *Dow Chem. Co. v. American Cyanamid Co., 2 USPQ2d at 1355.*

For the reasons of record and those set forth herein, Applicants respectfully request reconsideration and withdrawal of this rejection.

5. Claims 2 and 15 are asserted as allegedly being unpatentable over McLaughlin, Erich et al., Tadler et al., and Fisher et al. as applied to claims 1 and 14 above, and further in view of Chang et al. (of record) under 35 U.S.C. § 103(a). Applicants respectfully traverse this rejection.

The Examiner's discussion and Applicants' rebuttal of McLaughlin, Erich et al., Tadler et al., and Fisher et al. have been discussed *supra*. The Examiner sets forth at pages 11 of the Office Action that Chang et al. teach that in the absence of a clinically relevant amount of bacteria, blood is transferred to a recipient mammal. Specifically, the Examiner states that ~~"Chang et al. teach it is beneficial to screen blood to prevent contamination".~~

Applicants respectfully traverse this statement. Applicant reiterate that Chang is directed to the safety of transfer of modified hemoglobin blood substitutes (see column 4 at lines 10-30), *not* to a method of screening blood/blood product for clinically bacteria and found to be free of gram positive and gram negative bacteria for transfusions. Nor is it even directed to the detection of clinically relevant amounts of bacteria at all.

PAGE 17/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

The deficiencies of each of the McLaughlin, Erich et al., Tadler et al., and Fisher et al. publications cannot be cured by the deficiencies of Chang et al. Applicants respectfully request reconsideration and withdrawal of this rejection.

6. Claims 7 and 17 are asserted as allegedly being unpatentable over Tadler et al. (of record) and Fisher et al. (of record) under 35 U.S.C. § 103(a). Applicants respectfully traverse this rejection.

The Examiner's discussion and Applicants' rebuttal of Tadler et al. and Fisher et al. have been discussed *supra*.

It is Applicants' position for the reasons of record and those set forth above that one of ordinary skill in the art at the time the application was filed would not have had a reasonable expectation of success of arriving at the claimed invention by combining the teachings of Fisher et al. and Tadler et al. due to the overwhelming evidence that attempts to create a method for screening blood and blood products for clinically relevant amounts of bacteria throughout the 1990's had consistently failed. Thus, one of ordinary skill in the art at the time the application was filed would not have a reasonable expectation of success that producing the method as currently claimed would be a viable endeavor.

Applicants respectfully request reconsideration and withdrawal of the rejection.

---

7. Claims 8 and 18 are asserted as being unpatentable over McLaughlin (of record) in view of Erich et al. (of record) under 35 U.S.C. § 103(a). Applicants respectfully traverse this rejection.

The Examiner's discussion and Applicants' rebuttal of McLaughlin and Erich et al. have been discussed *supra*. Applicants respectfully request reconsideration and withdrawal of the rejection.

PAGE 18/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10

COPY

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: _____, 2003

COPY

Anita Varma
Reg. No. 43,221

Customer No: 28120
Docketing Specialist
Ropes & Gray, LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050

PAGE 19/38 * RCVD AT 12/3/2003 12:18:41 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7468000 * CSID: * DURATION (mm-ss):12-10